

REMARKS

Status of the Claims

By virtue of the Listing of Claims presented herein, claims 124, 132-137, 139-143, 145-150, 155-159, and 163-174 remain pending.

Claims 136, 137, 150, and 174 have been amended to replace the article, “A” in the preamble with the article, “The”, in order to enhance clarity.

Claims 145-149 and 155-159 have been amended to recite that the recited mammal exhibits a decrease in body weight. The amendments find basis, for example: at page 5, line 15, through page 6, line 2, which recites that “modulators of the present invention include nucleic acid molecules, including recombinant DNA molecules (e.g., cDNA or a vector containing the cDNA or isolated genomic DNA) ...”, which encode OB polypeptides as recited in the instant claims; and at page 7, lines 20-28, which recites that “[a]ll of the foregoing materials are to be considered as modulators of body weight,” and that the “the invention contemplates both diagnostic and therapeutic applications,... all contingent upon the use of modulators defined herein, including nucleic acid molecules and peptides,” and that “the modulation of body weight carries specific therapeutic implications and benefits, in that conditions where either obesity, or conversely, cachexia represent undesired bodily conditions, can be remedied by administration of one or more of the modulators of the present invention.”

Accordingly, no new matter is introduced by virtue of the amendments to the claims.

Claim Objections

The Examiner has maintained the previous objection to claims 136, 137, 150, and 174 on the grounds that they allegedly should begin with “The method of claim...” Applicant maintains that this objection is improper for the reasons set forth in Applicant’s response filed October 31, 2007. Nonetheless, and without acquiescing to the Examiner’s objections, Applicant has amended the claims to begin with “The method of claim...,” thereby rendering moot the maintained objection.

The Examiner has maintained the previous objection to claims 145-149 and 155-159 on the grounds that they allegedly do not clearly set forth that the mammal exhibits a decrease in

body weight or that the therapeutic effect is decrease in body weight. Applicant maintains that this objection is improper for the reasons set forth in Applicant's response filed October 31, 2007. Nonetheless, and without acquiescing to the Examiner's objections, Applicant has amended the claims to recite that the mammal exhibits a decrease in body weight, thereby rendering moot the maintained objection.

Because the amendments presented above obviate objections raised by the Examiner in a manner that is in accordance with the Examiner's suggestions, the amendments merely present the claims in better condition for appeal and do not require further search or consideration.

Claim Rejections

All arguments in all previous responses of record in the instant case, whether expressly indicated as such below or not, are hereby incorporated by reference and reapplied to the rejections set forth in the instant Office Action.

Rejection under 35 U.S.C. § 112, first paragraph: Enablement

Claims 124, 132-137, 139-143, 145-149, 155-159, and 163-173 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner continues to emphasize targeting of the claimed vectors to a particular tissue or cell type as the cornerstone of his rejection. As presented in Applicants' previous response(s) (see for example, the Response filed on October 31, 2007, herein incorporated in its entirety), it is notable that the Examiner's own characterization of references of record that are relevant to claimed methods, supports rather than negates, Applicant's argument that tissue or cell type targeting was not an essential feature of the claims at the time of the effective filing date, and therefore is irrelevant with respect to enablement of the instant claims. Furthermore, as Applicant discussed in previous response(s), as illustrated by the Examiner's synopsis of each of the Fletcher et al. (1995), Morsy et al. (1998), and Muzzin et al. (1996) references, these references also collectively demonstrate that, in fact, selection of any of several particular

combination of delivery, dosage, administration, etc. parameters may have been selected as taught in the instant application in order to achieve an effect as instantly claimed methods. Again, this negates the Examiner's assertion of lack of enablement based on the alleged teachings of these references.

For the reasons provided in previous responses (see for example, the Response filed on October 31, 2007), Applicants respectfully request the withdrawal of the rejection of the claims under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, first paragraph: new matter

The Examiner maintains the rejection of claims 124, 132-137, 139-143, 145-150, 155-159, and 163-174 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner again asserts that the phrase "operatively linked to a promoter" constitutes new matter.

This continued rejection is traversed, as in previous response(s) (see for example, the response to this rejection in the Response filed on October 31, 2007, hereby incorporated in its entirety). Applicants maintain that page 51, lines 1 through 3 of the specification states that "Transcriptional and translational control sequences are DNA regulatory sequences, such as promoter, enhancers, terminators and the like, that provide for the expression of a coding sequence in a host cell." Page 51, lines 5 through 8, states that "A coding sequence is 'under the control' of transcriptional and translational control sequences in a cell when RNA polymerase transcribes the coding sequence into mRNA, which is then trans-RNA spliced and translated into the protein encoded by the coding sequence." Thus, "a promoter" comprises a species within the genus of 'transcriptional and translational control sequences' as disclosed in Applicant's specification. Thus, a coding sequence that is "operatively linked to 'a promoter'" clearly falls within the scope of the meaning of a coding sequence that is "under the control" of a 'transcriptional control sequence'. Further, the term "operatively linked to a promoter" is an art-recognized phrase, the meaning of which is well within the purview of a person of skill in the art. Even assuming arguendo that this phrase is not art-recognized, it is well established that Applicant is allowed and entitled to be his own lexicographer. In this regard, the meanings ascribed to both phrases "

‘under the control’ of transcriptional and translational control sequences” and “promoters” render the meaning of the claim as amended, in view of Applicant’s teachings and knowledge in the art, readily apparent to the skilled artisan.

The Examiner again asserts that “the concept of an OB protein comprising ‘amino acids 22-167 of SEQ ID NO:4 wherein one or more amino acids selected from the group consisting of amino acids 53...166 is substituted with another amino acid’” in claims 134, 142, 148, and 158 is new matter. For the reasons presented in previous responses (see for example, the Response filed on October 31, 2007, herein incorporated in its entirety), this rejection remains traversed.

The instant specification, discloses, for example, that: (1) interspecies OB polypeptides homology is high, and as much as greater than 80% homologous (see, e.g., page 5, line 25, through page 6, line 2); (2) the primary sequences of mouse and human OB polypeptides identified in vivo and disclosed in full by Applicants (SEQ ID NOS: 2 and 4 respectively) share 83% amino acid sequence homology; also see e.g., Figure 4 and page 12, lines 15-23, as amended herein); (3) both mouse and human OB polypeptides (SEQ ID NOS: 2 and 4, respectively) are capable of modulating body weight when administered to ob/ob mice and wild-type mice (e.g., page 5, lines 6-14 and in the Examples, throughout); (4) OB-encoding polynucleotides of essentially the same size as the disclosed mouse OB polynucleotide sequence were isolated and identified based on high homology to an entire exon (SEQ ID NO:7) of the mouse OB-encoding sequence (see, e.g. Figure 16 and page 95, lines 9-21); (5) mouse and human OB polypeptide polymorphic forms exist in vivo, characterized by deletion of glutamine at position 49 (see, e.g., Figures 5 and 6, page 12, line 24 through page 13, line 8, and SEQ ID NOS: 5 and 6); (6) numerous exemplified amino acid positions that are not essential for activity may be substituted by numerous exemplified amino acids, based on the sequence alignments between mouse and human OB proteins, as well as on disclosed structural information (see, e.g., page 32, line 6, through page 35, line 23); and (7) each identified mouse and human polypeptide demonstrated to be cleaved to remove an N-terminal 21-amino acid signal sequence (see, e.g. pages 12 and 13, and Figures 3, 4, 5 and 6), assays for weight modulatory and food intake inhibition activity of OB polypeptides, and exemplary results obtained therefrom (see, e.g., Example 8 (pages 112-130), and Figures 28A-28D). Therefore, Applicant has described multiple

OB polypeptides possessing weight modulatory capability as a common functional feature, and possessing from zero (0) percent to 17% amino acid sequence variability, respectively (i.e., possess 100% and as little as 83% amino acid sequence identity relative to one another) as a common structural feature.

Accordingly, the inquiry with respect to item 1) above reveals that there is little substantial degree of variation between species within the claimed genus: the OB polypeptide amino acid sequences as recited in the claimed methods are capable of modulating body weight, and are described in the instant specification (SEQ ID NOS:2, 4, 5, or 6). Thus, contrary to the Examiner's assertion that "the specification is limited to specific amino acid difference (sic) at the positions claimed (except 56 and 95), and does not suggest substituting amino acids at the positions claimed with any amino acid as broadly claimed," is new matter, the degree of variation within the claimed genus is fully exemplified and described in the instant application as filed.

The assessment with respect to item 2) of the inquiry similarly reveals that the instant application describes a representative number of examples, either explicitly or implicitly, such that the skilled artisan would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species. In this regard, and as explained in previous responses as well as in the analysis above, the instant application provides an amino acid sequence alignment of mouse and human OB polypeptides, and indicates 28 positions at which differences between the sequences are observed, which translates to 83% sequence identity between the two sequences (see, e.g. Figure 4). Figure 4 thus inherently discloses, as the skilled artisan would recognize, OB polypeptides that differ from either the mouse or human sequence depicted in Figure 4 by one, two, three, four, five, six, seven, eight, nine, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 amino acids, corresponding to OB polypeptide sequences possessing 99.4%, 98.8%, 98.2%, 97.6%, 97.0%, 96.4%, 95.8%, 95.2%, 94.6%, 94.0%, 93.4%, 92.8%, 92.2%, 91.6%, 91.0%, 90.4%, 89.8%, 89.2%, 88.6%, 88.0%, 87.4%, 86.8%, 86.2%, 85.6%, 85.0%, 84.4%, 83.8%, or 83.0%, respectively. Thus, there can be no doubt that a representative number of species encompassed by the claimed genus are described, either explicitly or inherently, such that the skilled artisan would recognize that Applicant was in possession of the necessary

common attributes or features of the elements possessed by the members of the genus in view of the disclosed species. The Examiner, in his latest recapitulation of the rejection, does not rebut the above comments, which were provided in Applicant's previous response. Accordingly, the rejection remains erroneous and should be withdrawn.

The Examiner's next rejection, which is directed to "the concept of an OB protein comprising 'amino acids 22-167 of SEQ ID NO:4 wherein one or more amino acids selected from the group consisting of amino acids 53... 166 is substituted with another amino acid' in claims 134, 142, 148, and 158" alleges that such recitation remains new matter", insofar as the specification allegedly "does not suggest substituting the amino acids at the positions claimed with any amino acid as broadly claimed." The rejection remains traversed: the analysis described above, which the Examiner has failed to address, demonstrated written description support for the instant claims. The Examiner's comments with regard to Figure 4 are unavailing in this regard, as the Figure, as well as disclosure throughout the specification concerning substitution that may be made in the recited ob polypeptides, provide ample basis for the recitations (see, e.g., page 34, line 6, through page 35, line 23). Applicants respectfully request reconsideration and the withdrawal of the rejection.

The Examiner's next repeats the rejection directed to "the concept of an OB protein comprising 'amino acids 22-166 of SEQ ID NO:6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with another amino acid' ", as recited in claims 135, 143, 149, and 159, alleging again that this recitation constitutes new matter insofar as the specification allegedly "does not suggest substituting the amino acids in the Gln deleted mutants in Fig. 5 and 6, specifically with any amino acid as broadly claimed." The rejection remains traversed: the analysis described above yields the same result with respect to the claimed genus Gln deleted OB proteins. It is readily apparent that simply subtracting "1" from each amino acid position number as recited in claims 134, 142, 148, and 158 that comes after position 49, which corresponds to the Gln that is disclosed to be deleted in the ob polypeptides depicted in each of Figs, 5 and 6, yields the recited positions for substitution which correspond to the position recited in claims 134, 142, 148, and 158. Applicants respectfully

request reconsideration and the withdrawal of the rejection.

The Examiner again reiterates portions of the rejection of claims 166-173, allegedly that they constitute new matter insofar as the support argued by Applicants in previous responses (see for example, the Response filed on October 31, 2007) is not found in the specification. The remaining portion of the rejections remains traversed: support for rejected substitutions is found in the portions of the specification to which the Examiner was directed in previous responses (i.e., pages 32 through 35 – see page 27, lines 20-24 of response filed June 29, 2006).

Specifically, support for claim 166(g) regarding positions 118-166 is found in Figure 4 in conjunction with the disclosure at page 35, lines 11-12, which states provides an embodiment corresponding to the helix forming potential of the disulfide loop structure corresponding to amino acids 117 to 167, the disclosure at page 34, lines 14-19, which states that for “disulfide bonded loop analogs the cysteine residues must be maintained”, and page 113, lines 16-19, which demonstrates that mature ob polypeptide, in which in the only residues that are cysteine residues are at positions 117 and 167 as depicted in Figure 4, participate in a disulfide bond. Therefore, amino acid positions 118 through 166 are available for substitution within the recited analog, in accordance with the teachings of the instant application. As such the rejected recitation does not constitute new matter.

The Examiner has maintained his new matter rejections for claim numbers 167-173 on the basis that he cannot find the relevant recitations. Applicants wish to direct the Examiner to specific regions of the specification, level of specific Figure, and page and line number, with respect to: subparts (a); (b); (c); (d); (e); (f); and (g) of claim 166, the Examiner is again directed to, respectively: page 134, line 27, through page 35, line 2; page 35, line 2; page 35, lines 3-4; page 35, line 4; page 35, line 5; page 33, lines 7-8; and page 34, lines 5-11. With respect to: subparts (a); (b); and (c) of claim 170, the Examiner is again directed to, respectively: page 32, line 21-page 33, line 2, in conjunction with page 33, lines 11-14, which describes analogs as recited in the each of subparts (a); (b); and (c) of claim 170. With respect to: subparts (a); (b); (c); (d); (e); (f); and (g) of claim 171, the Examiner is again directed to inspect the disclosure found in the specification as outlined above for claim 166 in conjunction with that outlined above for 170. With respect to: subparts (a); (b); (c); (d); (e); (f); (g); and (h) of claim 173, the

Examiner is again directed to inspect the disclosure at page 54, line 24, through page 55, line 19, Figures 22A-22C and 22A-22B, and the amino acid sequences provided in the recited SEQ ID NOS, which collectively discloses the amino acid sequence of the recited tags/sequences (e.g., HIS-tags, remnants of KEX-2 or thrombin cleavage of exogenous, vector-derived (e.g., “non-OB”) sequences), and discloses that they may be fused to the N-terminus of an OB protein as recited in the claims. With respect to the subparts, (a) through (h)(8), of each of claims 169 and 172, the Examiner is again requested to inspect the portions of the specification outlined in the portions of the specification outlined for each of claims 166, 167, 168, 170, 171, and 173.

Accordingly, the rejection of claims 166, 167, 168, 169, 170, 171, 172, and 173 is in error and should be withdrawn. Each and every rejected claim recitations is supported in the indicated Figure and/or page-and-line citations as the Examiner (along with his supervisor, if necessary) will appreciate upon careful, competent (re)review of such citations.

Rejection under 35 U.S.C. § 112, first paragraph: written description

The Examiner maintains the rejection of claims 124, 132-137, 139-143, 145-150, 155-159, and 163-174 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement because the specification allegedly “does not provide written description for the ‘therapeutically effective amount’ of a vector administered to a mammal ‘such that the mammal exhibits a decrease in body weight.’” The Examiner continues to turn to page 83, line 4, to assert that the disclosure (and therefore the claims) is limited in scope by way of targeting human fat cells, in order to support the rejection. As previously discussed in the Response filed on October 31, 2007, herein incorporated in its entirety, the specification does not expressly or implicitly disclose that targeting of fat cells is the only administration modality by which the instantly claimed methods may be practiced; the cited portion states the “the ob gene could be introduced into human fat cells to develop gene therapy for obesity.” This statement does not negate any other targeting modality, including, to specific targeting of any tissue or cell type at all, as described above, in order to practice the claimed methods. Furthermore, it is well established that an Applicant’s claims to a disclosed invention is not bound by any suggested theory or mechanism for the inventions operation, even if such suggested theory is ultimately

found to be incorrect.

Furthermore, contrary to the Examiner's continued assertion, the instant specification provides ample description of determination of a therapeutically effective amount, of example at page 72, lines 5-9 and page 72, line 25, through 73, line 5, which discloses that a therapeutically effective amount comprises an amount sufficient to reduce a clinically significant deficit in the recited activity function, or response of the host by at least about 15 percent, at least 50 percent, by at least 90 percent, or to prevent such a deficit. A therapeutically effective amount is disclosed to alternatively comprise an amount sufficient to cause an improvement in a clinically significant condition in the host by, for example, these benchmark values. The instant application also discloses that treatment of, for example, abnormal elevation of body weight is a clinically significant condition for which a therapeutically effective amount of the recited OB-encoding vectors may be administered in the claimed methods in order to achieve a decrease in body weight (see, e.g., page 11, lines 5-8). Therefore the recitation of a "therapeutically effective amount" enjoys satisfactory written description support in the application as filed. Accordingly, for the reasons provided in previous responses as well as those provided herein, the rejection remains traversed.

Applicants believe that all issues raised in the Office Action have been properly addressed in this response and in the amendments to the claims as shown in the attached Listing of Claims. Accordingly, reconsideration and allowance of the instant claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

CONCLUSION

A petition for a two month extension of time is attached. No additional fees are believed due for this submission. However, if a fee is due, the Commissioner is hereby authorized to charge payment of any fees associated with this communication, to Deposit Account 19-4293 referencing Docket No. 16454.0005. Additionally, the Commissioner is hereby authorized to charge payment or credit overpayment of any fees during the pendency of this application to Deposit Account 19-4293.

Respectfully submitted,

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